The proteomic mapping and profiling of the proteome markers of membrane surface of the hematopoietic stem cell is a new biotechnological platform for early molecular-biologic diagnostics and alternative approach to the therapy of cancer, neurodegenerative and autoimmune diseases.

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Most of the fatal diseases are diagnosed only when it is almost impossible to help the patient. Such a neurodegenerative disorder (NDD) as the amyotrophic lateral sclerosis (ALS) is diagnosed only when 70% to 80% of motor neurons are dead, which is similar in the Alzheimer's disease (AD), dementia with Lewi bodies (DLB), Parkinson's disease (PD), systemic cortical atrophy (SCA), and other NDDs that are associated with the degeneration and atrophy of the specialized neurons in the cortex and other areas of the brain and spinal cord (SM). These diseases are also known as the disorders of accumulation because of the aggregation of the pathologic proteins as a result of mutations of certain genes. Accordingly, the motor neurons of FUS-proteins, SOD-1 proteins or TDP-43 proteins accumulate in the cytoplasm of the motor neurons in the ALS. The AD, SCA and ALS-dementias are also called tauopathies as the tau protein aggregates in the cortical neurons. In the Parkinson's disease the Lewi's bodies aggregate in the cytoplasm of the neurons of striatopallidal area of the brain. Cancer and malignant disorders form another group of the fatal diseases of civilization and the essence of their pathology lays the accumulation of cancer-specific proteins (CSPs) in the cancer cells (CCs) and cancer stem cells (CSCs). The diseases that have an autoimmune character (multiple sclerosis, type I diabetes mellitus, systemic lupus erythematosis, polymyosite) are also associated with the accumulation of various pathospecific proteins.

The accumulation of the molecules of the pathospecific proteins in the specialized cells of the tissues and detection of their circulation in the body fluids became the fundamental criterion for the methodology of early molecular-biologic diagnostics of these diseases. In the ALS, the molecular markers of neurofilaments in the cerebrospinal fluid (CSF) are tested for. In the case of cancer and other malignant tumors, the main criteria of early diagnostics are the tumor markers represented by the tissue-specific CSPs or CSPs containing microvesicules. Currently, over 200 markers of cancer are known but clinically only 15 to 20 markers of diagnostic value are diagnosed. Other tumor markers have no diagnostic value as they are not specific. Same holds true in the early diagnostics of the autoimmune diseases. Hence, early diagnostics of cancer and other malignancies as well as of the autoimmune and neurodegenerative diseases is based on the detection of the tissue-specific molecular protein markers of the damaged cells or their microvesicles (exosomes) in the tissues and biologic fluids. In other words, it is impossible to diagnose the disease at the molecular level until it acquires localization and tissue specificity. The molecules of the pathospecific proteins of the damaged cells appear in the body fluids rather late, only when their number in the cell becomes critical and the damage of these cells is pronounced and lethal for it. So, most of the fatal diseases are diagnosed only when the pathological process is advanced and almost incurable.

The global tendency for the earliest possible diagnostics relying on the detection of the molecular protein markers of the pathologic process in the biologic fluids is not the earliest opportunity to diagnose the disorder, as prior to it the cells should disintegrate and afterwards the protein markers appear in the biological fluids.

Our analysis of the pathogenesis of the studied diseases showed that they are always underlain by the disorder of the blood-tissular or blood-brain barrier induced by such etiologic factors as viruses, bacteria, injury, ischemia, hypoxia or other. The white blood cells (WBCs) of peripheral blood (PB)

penetrate the damaged tissue, initiate the clearing aseptic inflammation in it and then restore the cellular-humoral balance by the cytotoxic action of the pro-inflammatory cytokines onto specialized cells of the damaged tissue, their lysis and removal of the damaged fragments.

Although the cell accumulates toxic fragments in the cytoplasmic aggregates, these sanogenetic processes result in the clearing the tissue from the damaged cells and their fragments, as well as restoration of the homeostasis of the tissue and its normal functioning. However, the regulatory and sanogenetic activity of the WBCs in the damaged tissue does not always end that successfully. Frequently, the WBCs are unable to change the fate of the damaged tissue and the regional stem cells (rSCs) as well as the hematopoietic stem cells (HSCs) have to assist them. Due to the universal regulatory mechanism of the horizontal and vertical proteomic informational exchange of the rSCs, HSCs and pathological cells, the latter achieve the phase of apoptosis or die immediately, while the former acquire certain amount of pathospecific proteins in their cytoplasm. These proteins considerably modify the structure of the intracellular signaling pathways and lead to the genetic and epigenomic changes in them. Such "immunization" of the HSCs and rSCs with the pathospecific proteins can result in the development of the CSCs from the HSCs or rSCS or in the genome or post-genome transformation of the molecular structure of the immunocompetent cells (ICCs), HSCs and rSCs. The modifications of the genomic-transcriptomic-proteomic structure of the HSCs lead to the hereditary disorders of the genetically determined affector functions and onset of the specific chronic insufficiency of the immune system (CIIS). The isolated pro-tumor CIIS forms in cancer and other malignancies while other protective functions (antiviral, antibacterial, antifungal and other) of the immune system remain intact, and the hyporeactivity of the HSCs and the immunocompetent cells (ICCs) of the immunity to the CCs, CSCs loss or reduced control over the number of the CCs and HSCs forms and results in the malignant growth ("plus tissue" phenomenon). Meanwhile, in the neurodegenerative and autoimmune diseases, the pathospecific CIIS forms, which is characterized by the hyperreactivity and aggression of the ICCs of the immunity to the specialized cells of the systemically organized tissues. The outcome of this type of the CIIS is the degeneration and atrophy of this tissue ("minus tissue" phenomenon). The neurospecific CIIS forms in the case of the NDDs, while the autospecific CIIS forms in the case of the autoimmune diseases. However, the immunodeficiency is not equal to the CIIS. The immunodeficiency manifests in the quantitative disorders of the cellular and humoral components of the immunity, and the CIIS manifests in the qualitative disorders of the genomic, epigenomic, mitochondrial, cytoplasmic and membrane structures of all ICCs and, primarily in the disorders of methylation of the HSCs as the systemic integrator of the hemopoiesis and immunopoiesis. So, the earliest possible diagnostics of cancer, NDDs and autoimmune diseases can be achieved through the diagnostics of the types of CIIS represented by the post-genomic (proteomic) disorders of the proteomic profile of the HSCs.

We propose a universal method of early molecular-biologic immunospecific diagnostics of cancer and/or neurodegenerative and autoimmune diseases that involves the immunophenotyping of membrane antigens (CD-markers) of the HSCs (CD34+ CD45+ HLA DR+) with consequent mapping and profiling of the received protein expression of the membrane surface (PEMS) of the HSCs of the tested subject and comparison of this profile with the identical values of the profile of the PEMS of the HSCs that represents the norm for a statistically significant group of healthy donors of bone marrow (54 people). If the comparative analysis of the normal profile of CD markers of HSCs and those of the tested subject shows diversity in the expression of six or more CD-markers, then the cancer-specific, neuro-specific or auto-specific CIIS can be diagnosed independently on the clinical and neurophysiologic manifestations of the neurodegenerative or autoimmune diseases.

The proteomic profiles of the PEMS of the HSCs are received in the multi-color flow cytometry in the CD34+ CD45+ gate of the HSCs with standard antibodies to the membrane antigens. The HSCs are obtained from the bone marrow sample of the tested subject or are mobilized from their peripheral blood after three days administration of the granulocyte colony-stimulating factor (G-CSF).

In case the comparative analysis of the examined and normal PEMS profiles shows overexpression of the CD81+ marker and hypoexpression of CD38+, CD33+, CD71+, CD90+, CD56+, CD19+, CD28+, CD300+ and CD2+, the cancer-specific PEMS profile is diagnosed. That implies excessive numbers of the CSCs and CCs in the subject independent on the tissue-specific commitment of tumor. In case the comparative analysis of the examined and normal profiles shows hypoexpression of HLA DR+, CD38+, CD13+, CD71+, CD117+, CD90+, CD50+, CD19+ markers and overexpression of CD56+, CD61+, CD2+, CD7+ and CD81+ markers, the NDD-specific profile can be diagnosed independent on the clinical and/or neurophysiologic manifestations of neurodegeneration. The pattern is the same when the HSCs are profiled for autoimmune diseases.

The method permits diagnostics of the proteomic signs of the disease in the relatives of the patients even without the clinical signs of the disorders. The method is developed on the basis of the analysis of the HSCs of 560 cancer cases (256 children and 250 adults), 120 NDD cases (66 ALS cases, 15 AD cases, 10 cases of SCA and 10 of PD), as well as 22 cases of various autoimmune diseases (10 cases of systemic lupus erythematosis and 12 cases of rheumatism).

The proposed method can become a fundamental diagnostic platform for early molecular-biologic diagnostics of the fatal diseases of civilization and opens up new strategies for the development of the technologies for complete cure at the earliest possible stage. New theoretic and methodologic understanding of the diseases of civilization as of the diseases associated with post-genomic (proteomic) damages of the HSCs allows for new understanding of the methods and stages of their treatment. Primarily, the therapy should begin with the arrest of the systemic reason of the disease by means of the molecularly targeted therapy or allogeneic transplantation of the bone marrow to replace the damaged HSCs with healthy cells. Also, the autologous HSCs can be transplanted but only after their direct reprogramming with small molecules from healthy somatic cells (fibroblasts, olfactory cells and other). The second stage can be the regenerative therapy of the available damages of the organs and tissues using all means of the regenerative medicine including cell therapy.